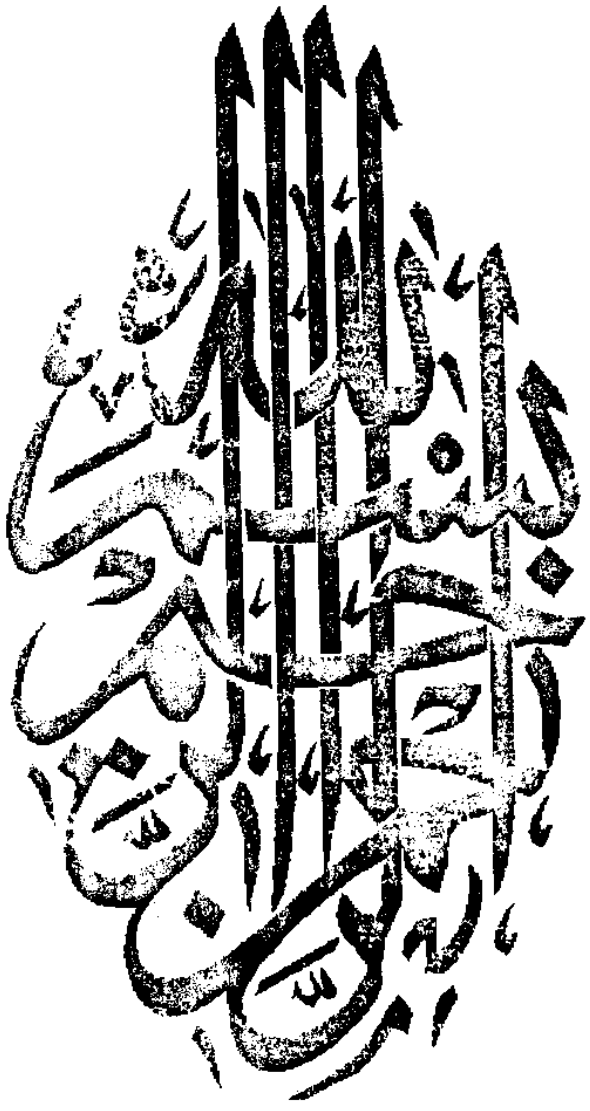

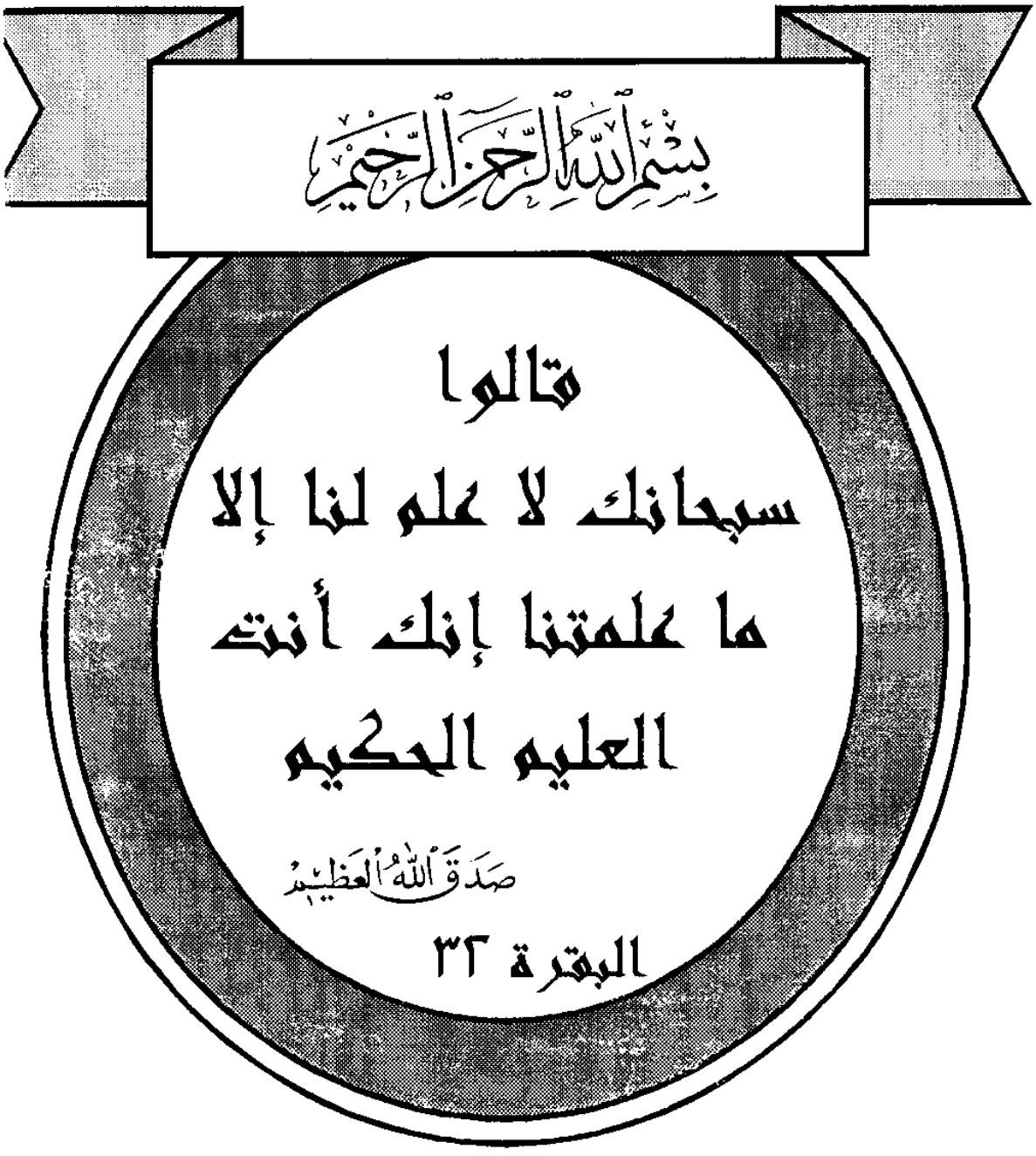

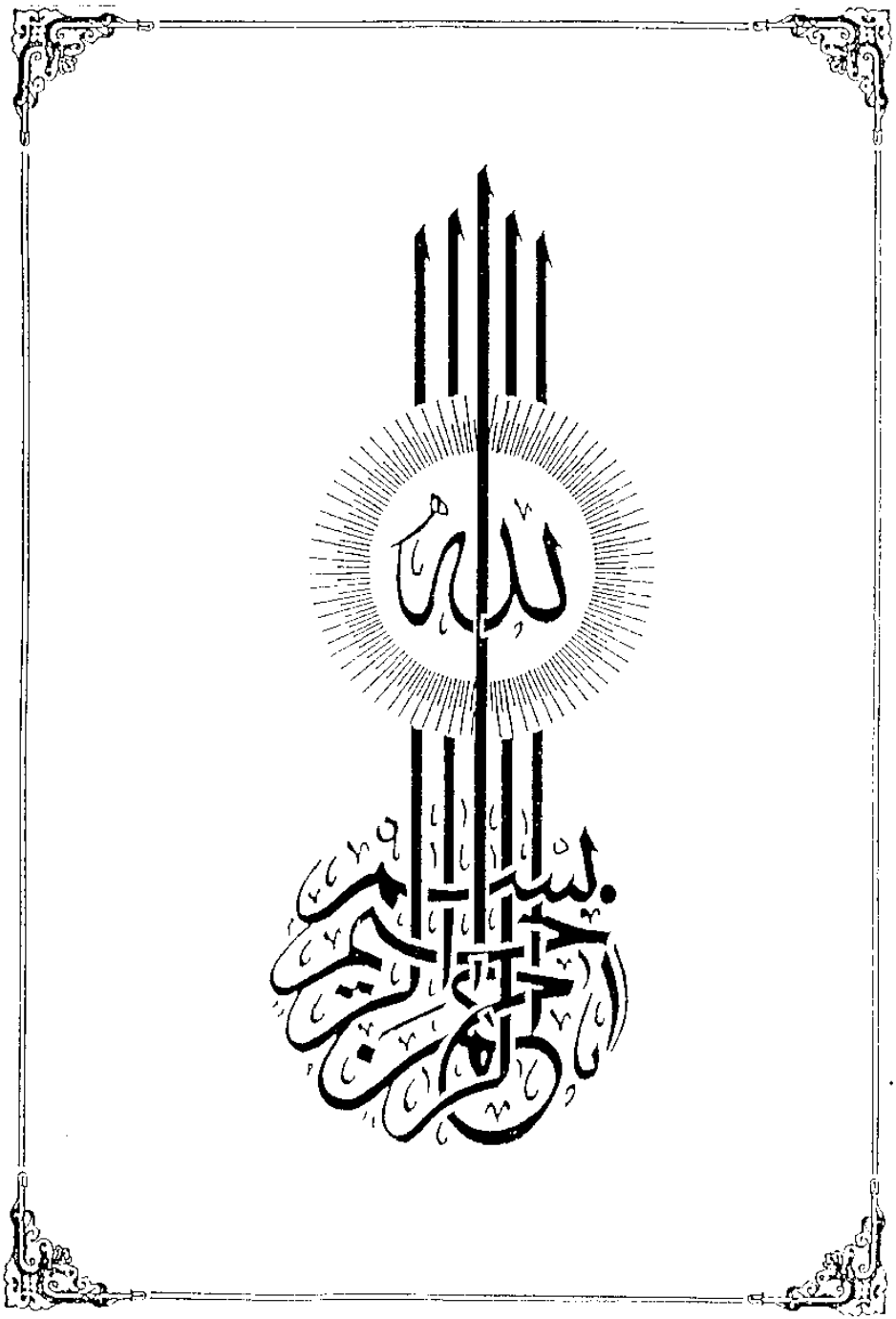

Acquired Hyperpigmentation *and* Therapeutic Modalities

Essay submitted in the partial
fulfillment of the Master degree in Dermatology

By

Lamya Mohamed H. Labib
M.B; B.CH

Under Supervision of:

Prof. Dr. Nadia Saleh
Ass. Prof. of Dermatology
Faculty of Medicine, Cairo Univ.

&

Prof. Dr. Moustafa Abou El-Ella
Assistant. Prof of Dermatology
Faculty of Medicine, Cairo Univ.

Faculty of Medicine, Cairo University

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Normal pigmentation of the skin is influenced by the amount and depth of melanin , by the degree of vascularity , by the presence of carotene and by the thickness of the horny layer (Arnold et al . , 1990) .

Both white and Negro skin contain the same number of melanocytes ; the difference in pigmentation results from greater melanocytic activity in darker skin , which is under the control of melanocyte stimulating hormone (MSH) of the anterior pituitary gland , and according to the size and location of the melanosomes . There are receptors on the surface of pigment cells for MSH and also to ACTH which is similar to MSH in the arrangement of the first 13 amino acids . Estrogen and progesterone also increase pigmentation through cyclic AMP which increases tyrosinase activity and so increases melanin formation and transfer (Julian Verbov , 1974) .

Hyperpigmentation can be classified according to increase in melanin (hypermelanosis) or non - melanin hyperpigmentation . Hypermelanosis can be classified according to :

A : The extent , whether diffuse or localized (patchy) .

B : The depth , whether in the epidermal layer when the skin appears more brown , or in the dermal layer , and the skin will show

a slaty grey or blue appearance . It could be differentiated whether dermal or epidermal by using wood's lamp (Bleehen et al . , 1992c) .

C; The etiological factors whether intrinsic or extrinsic (Burton , 1990) .

Methods of treatment of hyperpigmentation include preventive methods as local sun - screens and therapeutic agents as Tretinoin , Hydroquinone , and Azelaic acid (Deleo and Maso , 1993) .

Also , the development of many new laser systems has provided the cosmetic surgeon? with ever increasing opportunities to provide patients with the best possible results in the management of a wide range of different aesthetic problems , and more advances are promised for the future (Wheeland , 1995) .

Aim of the work :

The aim of this essay is to review the most common causes of acquired hyperpigmentation and to discuss the different therapeutic modalities used to treat or decrease this hyperpigmentation .

Normal Pigmentation of The Skin

Normal pigmentation of the skin is influenced by the amount and depth of melanin , by the degree of vascularity , by the presence of carotene , and by the thickness of the horny layer (Arnold et al. , 1990) .

Melanin :

Melanin has been described , and some of its known mechanisms of action have been indicated by Menen and Haberman (1977) . It is a remarkable compound able to protect susceptible tissues from enormous doses of ultraviolet radiation , not apparently by absorption , but also by some as yet unclear active reactions with ultraviolet rays (Stewart et al. , 1978) .

The main function of melanin is to protect the cell nuclei from damage by ultraviolet rays which would otherwise damage the DNA molecule (Burton , 1990) . Melanin is the pigment produced by differentiated pigment cells or melanocytes (Abdel - Malak , 1988) .

Melanocytes :

Embryology and site :

Melanocytes , found chiefly in the basal layer of epidermis , are derived embryologically from the neural crest (Julian Verbov , 1974) . Melanocytes are derived from a stem population of melanoblasts that originate of neural crest cells soon after closure of the neural tube . Emigration of melanoblasts from this embryonic source begins as early as two and half weeks gestation in human embryos . These early neural crest cells are committed to differentiate into melanocytes either before or during their migration out of the neural tube . This has been demonstrated by the success in developing pure cultures of melanocytes from mechanically and enzymatically isolated neural tubes . In vivo , the melanoblasts of most species begin melanization just before or just after they have reached their distination . At birth , melanocytes are well - established in the epidermis and transfer melanosomes to keratinocytes . These melanocytes remain in the basal layer of epidermis and rarely divided or migrating away . The melanocytes that remain in the central nervous system are found in the leptomeninges , uvea , or retina (Stewart et al. , 1978 and Boissy , 1988) .

Uveal melanocytes are also well - established in the choroid , ciliary body , and iris at birth . Pigment synthesis in these melanocytes begins during late gestation , 140 days , and by birth , the uveal melanocytes

have almost completed their quota of melanosomes . However , the uveal melanocytes may still be melanogenically active at birth .

The cutaneous melanocytes differ dramatically from the uveal melanocyte in the duration of time they are involved in melanization . Melanocytes of the epidermis are continuously synthesizing melanosomes and transferring them to keratinocytes throughout life . These melanocytes are found exclusively in the basal layer of the epidermis ; in fact ; the ventral side of the perikaryon frequently appears to dip down into the dermis pendulously , while still resting on a basement membrane . The dendrites of these basal melanocytes reach - up intercellularly through the epidermis to the stratum spinosum . The melanocyte is loosely anchored in this position .

Forms of intercellular contact with keratinocytes by desmosomes and gap junction , or attachment to the basement membrane by hemi - desmosomes do not exist in the melanocyte . Also of interest is the absence of dermal anchoring fibrils beneath the melanocytes proper (Boissy , 1988) .

Number of melanocytes :

The melanocytes that do gain the epidermis are fairly uniformly distributed in numbers , surprisingly similar for all races (Stewart et al . , 1978) .

The quantity of melanocytes per area of skin at various body sites in the human varies dramatically (about three fold) ; however the whole body average ranges from 800 to 1600 / mm^2 . The quantity of melanocytes per area decreases with age (Biossy , 1988) . This means that both white and Negro skin contain the same number of melanocytes , the difference in pigmentation resulting from the greater melanocytic activity in darker skin and size and location of melanosomes (Julian Verbov , 1974) .

Shape of Melanocytes :

In its mature form , this highly social octopus - like cell , surrounded by its group of keratinocytes , has no known function beyond pigment (melanin) production and transference . Some of the melanocytes are dendritic and pass on the pigment packages through hollow tubes dendrites to the surrounding epidermal cells . On the same time the melanocytes that remain in the neural crest are not dendritic and retain melanin they produce (Stewart et al . , 1978) .

Dendrite formation is stimulated by melanogenic factors such as cyclic AMP (cAMP) and melanocyte stimulating hormone (MSH) . The formation of dendrites is not unique to pigment cells . Neuroblastoma cells , which also originate from the neural crest , develop dendrites , a phenomenon regarded as a sign of cellular differentiation (Abdel - Malak , 1988) .

In Hx & E stained sections melanocyte has a small dark nucleus and clear cytoplasm . It can be stained black with Fontana Masson (silver) as it contains melanin , and more specifically with Dopa reaction as it possesses the ability to form melanin (tyrosinase containing cell). Melanocytes present in hair root papillae also enjoy the active participation of cortical and medullary keratinocytes in transference of pigment to the hair shaft (Burton , 1990) .

The use of antibodies against S - 100 protein provides another staining method for identification of melanocytes . S - 100 protein is an acidic protein that binds Ca^{++} and Zn^{++} . It was called S - 100 because of its solubility in 100 % ammonium sulfate at neutral pH . It is found in the cytoplasm and in the nucleoplasm . It seems to be involved in the regulation of the diffusion of monovalent cations across membranes . It seems to have a stimulatory effect on the RNA polymerase I activity in nuclei . This function may explain the presence of S -100 protein in a large variety of cells and melanocytes . The most useful application of the antibody against S-100 protein includes :

(1) Diagnosis of spindle cell melanoma .

(2) Distinguishing between melanocytes and lymphocytes in halo nevi (Lever , 1990) .

Melanocytes behave as a unicellular glands (a phenomenon known as

cytocrine activity) , which produce the melanosomes and transfer them to the surrounding keratinocytes (Bolognia and Pawelek , 1988) .

Melanosomes are membrane bound organelles located in the cytoplasm of melanocytes and bearing tyrosinase enzyme . They are the organelles of melanin synthesis and transfer it from melanocytes to the surrounding keratinocytes . The more melanin they accumulate the denser they appear under the electron microscope . Melanosomes contain :

(1) Structural matrix proteins ,

(2) Tyrosinase enzyme which catalyzes the first step in melanin synthesis ,

(3) Proteins of unknown structure and function .

Tyrosinase is synthesized on the cell organelles (ribosomes and smooth endoplasmic reticulum) and then it is stored in small vesicles . Fusion of the vesicles to the structural proteins results in the formation of a melanosome . The structural proteins form a lamellar matrix within the melanosome upon which melanin is deposited . Melanosomes go through four stages of development :

* Stage I : melanosomes are spherical and may contain filaments .

* Stage II : melanosomes are oval in shape and contain parallel longitudinal filaments . There is no melanin deposition at this stage .

* Stage III : melanosomes have a high level of tyrosinase activity and